UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

TO: Ralph C. Wright, PM
SPRD (TS-791)

THROUGH: Orville E. Paynter, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Linuron Risk Assessment, Statistical Aspects of

Toxicological aspects of the animal studies supporting reregistration of Linuron are reviewed in J. Holder's memorandum to Ralph C. Wright dated 15 September 1982. That memo and one from R.C. Wright, Linuron Risk Assessment, dated 14 September 1982, have indicated the need for a statistical evaluation of the oncogenic potential of Linuron expressed by the interstitial testicular tumor findings in Haskel Laboratory Report No. 100-80 of a long-term Linuron (INZ-326) feeding study in CHR-CD, Sprague-Dawley rats.

Survival of male rats and relevant tumor pathology is displayed in Table 1 for the 70 animals per dose (0, 50, 125 and 625 ppm Linuron) surviving one year. The study design allocated 80 animals to each sex-dose group with an interim kill at the end of 1 year. Our analysis begins with the 70 animals per group surviving at 1 year as the first death on study occurred at day 378 and the first death with interstitial testicular tumor occurred on day 443 (both of these animals were in the high dose group). All 280 males contribute information to the survival analysis but 17 of the 125 deaths on study and 1 of the 155 animals surviving to final kill are deleted from the analyses of the interstitial tumor rates due to lack of usable testicular pathology specimens.

The data in Table 1 clearly indicate no suggestion of a dose-related decrease in survival of study rats. Evaluation of summary data using X^2 test for homogeneity (a two-tail hypothesis of no difference among the four groups against the alternative that they differ in some way) indicates statistical significance at the p = .012 level of test for the (1/31, 3/24, 5/31 and 8/22) deaths during study and p <.01 for those examined at final kill. In Table 1 we show that, using Peto's prevalence test of positive trend, that ther is a Linuron dose-related increase in the rate of interstitial testicular tumors diagnosed after 18 months. This trend is significant at p <.0002 level of test for animals dying on study and at p <.0001 for those examined at final kill.

Using the total study results shown in Table 1 we have conducted low-dose risk extrapolations by the following mathematical models: Multi-stage (Crump); Multi-hit and One-hit (Rai and Van Ryzin); both independent and additive versions of the Probit, Logit and Weibull models (Kovar and Krewski, Dores' 81 Program). None of these models provided adequate fit to the data (p <0.6 by goodness of fit tests) when the complete data set was used. However following the recommendation of the EPA Cancer Assessment Group and Mantel, et. al. we deleted the high dose results and obtained a virtually perfect fit using the Multi-Stage Model (Global '79 by Crump.) The goodness-of-fit obtained by using the dose expressed in ppm and mg/kg/day in rats and mg/kg/day in man were similar and the results reflect only a scaling of the dose-response curves.

Estimates obtained by fitting the control, low and mid-dose response rates (4/68, 9/62 and 19/65) to the human dose equivalents of 0, 0.5 and 1.25 mg/kg/day by the multi-stage model are shown below:

Model $p = 1 - e^{[-(0.0606246 + 0.16866\ dose + 0.047548\ dose^2)]}$

Potency Estimate $Q_1^* = 0.328$

Attributal Level of Oncogenicity Risk	Estimates of Virtually Safe Dose: Maximum Likelihood Estimate	Lower 95% Confidence Bound
1×10^{-1}	5.419×10^{-1}	3.07×10^{-1}
1×10^{-2}	5.862×10^{-2}	3.05×10^{-2}
1×10^{-3}	5.922×10^{-3}	3.04×10^{-3}
1×10^{-4}	5.928×10^{-4}	3.04×10^{-4}
1×10^{-5}	5.929×10^{-5}	3.04×10^{-5}
1×10^{-6}	5.929×10^{-6}	3.04×10^{-6}
1×10^{-7}	5.929×10^{-7}	3.04×10^{-7}
1×10^{-8}	5.929×10^{-8}	3.04×10^{-8}

Using TMRC of 0.005628 mg/kg/day the MLE for extra risk is 9.5×10^{-4} and the upper 95% Confidence Bound on the extra risk is 1.85×10^{-3}.

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* To scale ppm in rat to mg/kg/d in rat we follow Lehman's Tables and divide by 20.

To scale mg/kg/d in rat to mg/kg/d in man we divide by the surface area adjustment recommended by Mantel & Scheiderman (JNCI 1975), i.e., (Human body weight in mg - animal body weight in mg)1/3.

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Attachment

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Table 1

Interstitial Cell Tumors in Sprague Dawley Rat Testicles

Part A: Trends

Dose in PPM	Days on Study # TBA/# With Tissue Exam 366-569	570-660	661-730	Sub-Total	(730+) Final Kill	Total Study
0	0/10	1/10	0/11	(1/31)	3/37	(4/68)
50	0/6	1/8	2/10	(3/24)	6/38	(9/62)
125	0/5	2/13	3/13	(5/31)	14/34	(19/65)
625	1/8	3/7	4/7	(8/22)	29/45	(37/67)
T stat.	420.69	996.053	1,548.17	2,964.9	7,797.9	10,764
Var.	69,227.1	290,095	339,280	698,602.1	2.334×10^6	3.033×10^6
Z	1.599	1.849	2.658	3.547	5.104	6.18
P	0.0549	0.032	.004	<.0002	<.0001	<.0001

Part B Survival & Losses

Dose	# Without Useful Pathology/No. Surviving At End of Interval					
0	0/60	1/49	1/37	(2)	0/37	(2)
50	0/64	2/54	5/39	(7)	1/39	(8)
125	5/60	0/47	0/34	(5)	0/34	(5)
625	0/62	3/52	0/45	(3)	0/45	(3)